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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,772	02/25/2002	Peter Droge	DEBE:008US	4391

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,772	DROGE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003 and 15 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-60* is/are pending in the application.

4a) Of the above claim(s) *52-57,59 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-51 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/3/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-60 are pending in the present application.

Applicant's election **without traverse** of Group I (claims 29-51 and 58), drawn to a method of sequence specific recombination of DNA in a eukaryotic cell, wherein the method is performed in a cell culture (or *ex vivo*), in the Amendment filed on 8/29/03 is acknowledged.

Accordingly, claims 52-57 and 59-60 are withdrawn from further consideration because they are drawn to non-elected inventions.

Therefore, claims 29-51 and 58 are examined on the merits herein.

Priority

The foreign application GERMANY 199 41 186.7 filed on 8/30/1999 has not been provided with the present application. Accordingly, the instant claims are given a priority date of 08/29/00.

Claim Objections

Claim 58 is objected to because the term "A eukaryotic cell" contains a eukaryotic cell present in vertebrate organism, including a human, which is drawn to a non-elected embodiment. The term - - An isolated eukaryotic cell - - should obviate this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-51 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the claims are drawn to an *ex vivo* method of sequence specific recombination of DNA in a eukaryotic cell, said method comprising: (a) providing said eukaryotic cell, said cell comprising a first DNA segment, said first DNA segment comprising an *att*B sequence according to SEQ ID NO:1 or a derivative thereof, an *att*P sequence according to SEQ ID NO:2 or a derivative thereof, an *att*L sequence according to SEQ ID NO:3 or a derivative thereof, or an *att*R sequence according to SEQ ID NO:4 or a derivative thereof, (b) introducing a second

DNA fragment into said cell, wherein if said first DNA segment comprises an *att*B sequence according to SEQ ID NO:1 or a derivative thereof, said second DNA segment comprises an *att*P sequence according to SEQ ID NO:2 or a derivative thereof, wherein if said first DNA segment comprises an *att*P sequence according to SEQ ID NO:2 or a derivative thereof, said second DNA segment comprises an *att*B sequence according to SEQ ID NO:1 or a derivative thereof, wherein if said first DNA segment comprises an *att*L sequence according to SEQ ID NO:3 or a derivative thereof said second DNA segment comprises an *att*R sequence according to SEQ ID NO:4 or a derivative thereof, or wherein if said first DNA segment comprises an *att*R sequence according to SEQ ID NO:4 or a derivative thereof said second DNA segment comprises an *att*L sequence according to SEQ ID NO:3 or a derivative thereof; and wherein said cell further expresses a bacteriophage lambda integrase Int, which induces sequence specific recombination through said *att*B and *att*P or *att*R and *att*L sequences; and a eukaryotic cell obtainable from the same method.

The instant specification is not enabled for the presently claimed invention for the reasons discussed below.

1. The breadth of the claims

With respect to the elected invention, the claims are drawn to an ex vivo method of sequence specific recombination of DNA in any eukaryotic cell, said method comprising (a) providing said eukaryotic cell a first DNA segment comprising an *att*B, an *att*P, an *att*L or an *att*R sequence having the limitation recited in claim 29, (b) introducing a second DNA segment into said cell, wherein the second DNA segment

has the limitation recited in claim 29, and wherein said cell further expresses any bacteriophage lambda integrase Int, which induces sequence specific recombination through said *att*B and *att*P or *att*R and *att*L sequences, and any eukaryotic cell obtainable from the same method.

2. The state and the unpredictability of the prior art

At about the filing date of the present application (8/29/2000), virtually nothing was known in the prior art on the *att*B sequence of SEQ ID NO:1 or a derivative thereof, the *att*P sequence of SEQ ID NO:2 or a derivative thereof, the *att*L sequence of SEQ ID NO:3 or a derivative thereof or the *att*R sequence of SEQ ID NO:4 or a derivative thereof or any bacteriophage lambda integrase Int that is capable of recognizing and inducing sequence specific recombination through the aforementioned *att*B and *att*P or *att*R and *att*L sequences as evidenced by the teachings of Nash, H.A (Ann. Rev. Genet. 15:143-167, 1981) and Hartley et al. (U.S. Patent 6,277,608). Furthermore, on the basis of the instant disclosure, it is apparent that SEQ ID NO:1 and SEQ ID NO:2 represent 5' end and 3' end PCR primer sequences respectively for cloning Int genes (see specification, page 21, line 22 continues to line 4 of page 22), and that they contain no essential structural features that constitute *att*B and *att*P sequences known in the art. It is also apparent from the present application, that SEQ ID NO:3 and SEQ ID NO:4 represent sense and antisense PCR oligonucleotides for the construction of a modified *att*P* site (see specification, page 22, lines 15-19), and that they have no essential structural features that constitute *att*L and *att*R sequences known in the art. As such, it would be unpredictable to know if any bacteriophage *lamba* integrase known in the art

would recognize the *att*B, *att*P, *att*L and *att*R sites and their derivatives as recited and that it mediates a sequence specific recombination of DNA in any eukaryotic cell *ex vivo* as contemplated by Applicants.

The physiological art has been recognized as unpredictable (MPEP 2164.03). This unpredictability is highlighted by the results reported by Lorbach et al. (J. Mol. Biol. 296:1175-1181, March 2000, IDS) showing the unexpected absence excision recombination at the genomic target sites in BL60 and HeLa reporter cell lines stably transfected with a single copy of pGFP*att*L/*att*R even in the presence of expression vectors pKEXInt-h or pPGKInt-h (page 1178, col. 2, second full paragraph).

3. The amount of direction or guidance provided

Apart from the disclosure that SEQ ID NO:1 and SEQ ID NO:2 represent 5' end and 3' end PCR primer sequences respectively for cloning Int genes (see specification, page 21, line 22 continues to line 4 of page 22) and SEQ ID NO:3 and SEQ ID NO:4 represent sense and antisense PCR oligonucleotides for the construction of a modified *att*P* site (see specification, page 22, lines 15-19), the instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use the aforementioned SEQ ID NOs and/or their derivatives (e.g., which mutations from a minimum of 1 up to 6 according to the definition on page 6, lines 9-12; and in which combinations) as *att*B, *att*P, *att*L and *att*R recombination sites that are recognized and catalyzed by a bacteriophage *lambda* integrase Int. As the prior art at the filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so.

Even with the proper *att* sites provided in a eukaryotic cell, it is further noted that the instant specification teaches specifically that **the wild-type Int was inactive** for catalyzing intramolecular integrative recombination in human reporter cell line BL-60 (see page 30, lines 8-14), and that **none of the utilized Int including the mutants Int-h and Int/218 BL60 was able to mediate excision recombination at the genomic target sites** in both human HeLa and BL-60 reporter cell lines stably transfected with a single copy of pGFP*att*L/*att*R (see page 30, lines 15-25). Then how is it reasonable to expect that a skilled artisan would be able to make and use any bacteriophage *lambda* integrase Int, to induce sequence specific recombination in the method as claimed even if the eukaryotic cell is provided with the proper *att*B and *att*P or *att*R and *att*L sequences without undue experimentation?

4. The quantity of experimentation provided

The instant specification fails to provide any example in which a sequence specific recombination of DNA in any eukarytic cell has been attained using a eukaryotic cell having a first DNA segment and a second DNA fragment having the *att*B, *att*P, *att*L and *att*R sequences as recited or any eukaryotic cell obtained by the same.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art as well as the art on the specific sequence recombination art using a bacteriophage *lambda* integrase Int in a eukaryotic cell, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 and its dependent claims 50-51 recite the limitation "after the steps (a)-(c)" in line 2 of claim 49. There is insufficient antecedent basis for this limitation in these claims. This is because in claim 29 from which claim 49 is dependent, there is no step (c). The metes and bounds of the claims are not clearly determined.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER